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EXAMINER

SASAN, ARADHANA

ART UNIT

PAPER NUMBER

1615

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/524,913	<b>Applicant(s)</b> DITTRICH ET AL.	
	<b>Examiner</b> ARADHANA SASAN	<b>Art Unit</b> 1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 23 October 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 12-17 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 12-17 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                    | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)         | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                          |

**DETAILED ACTION**

***Status of Application***

1. The remarks, amendments, and Request for Continued Examination filed on 10/23/09 are acknowledged.
2. Claims 1-11 were cancelled. Claim 12 was amended.
3. Claims 12-17 are included in the prosecution.

***Continued Examination under 37 CFR 1.114***

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/23/09 has been entered.

***MAINTAINED REJECTIONS:***

The following is a list of maintained rejections:

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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6. Claim 12 **remains** rejected under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Domb (US 2004/0057970 A1).

The claimed invention is a biodegradable, plastic viscous antitumor composition with prolonged release of an antitumor agent for administration into tissues, comprising: at least one antitumor agent being distributed in a carrier, the carrier being plastic viscous and consisting of biodegradable oligoester, having the numeric mean relative molecular mass  $M_n$  from 650 to 7,500, the mass mean relative molecular mass  $M_w$  from 800 to 10,000 and the glass transition temperature  $T_g$  from -35 to 45°C, and which is prepared by polycondensation reaction of polyhydric alcohol containing at least 3 hydroxy groups with at least one aliphatic  $\alpha$ -hydroxy acid in the molar ratio of polyhydric alcohol to aliphatic  $\alpha$ -hydroxy acid being from 0.5:99.5 to 12:88, wherein the essential molecule of biodegradable oligoester is a polyhydric alcohol, to the hydroxy groups of which chains created from several molecules of at least one aliphatic  $\alpha$ -hydroxy acid are bound by ester bonds, and being in the form of homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion.

Domb teaches a "liquid polymeric implant, made of biodegradable polymer matrix loaded with an anticancer agent. The effective anticancer agent, Cisplatin or Paclitaxel, is homogeneously dispersed into the polymer matrix. The active drug is released in a controlled manner to the surrounding tissue, when placed in contact with body fluids, while the polymer carrier is eliminating itself by slow degradation. The implant in a form of ...liquid polymer... or injectable microspheres is injected into the tumor ... The

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implant is providing a high dose of anti-cancer drug for an extended period of time, in the tumor site, with minimal systemic drug distribution, thus, providing a localized treatment of the residual tumor cells as a complementary drug therapy to the surgery” (Page 4, [0046]).

Domb does not expressly teach the anticancer agent distributed in a biodegradable oligoester carrier prepared by a polycondensation reaction.

Hampl teaches oligoesters, specifically, a terpolymer (GA-M-DLLA) of DL-lactic acid (LA), glycolic acid (GA) and mannitol (MA), a copolymer DL-lactic acid and mannitol (M-DLLA) and lactide-glycolide copolymers (DL-PLGA) (Abstract). The GA-M-DLLA was prepared by the polycondensation reaction (Page 108, 2.2 Preparation of oligoesters) of LA (45.05 mol), GA (45.06 mol) and MA (0.9 mol) and has a  $T_g$  of 20°C,  $M_n$  of 2.20Kda and  $M_w$  of 3.95 kDa (Page 108, Table 1). Bovine serum albumin (BSA) was the active ingredient entrapped in microspheres prepared with the terpolymer of GA-M-DLLA which depicted prolonged release of BSA over 15 weeks (Abstract and Figures 4 and 5). The microspheres were administered subcutaneously to mice (Page 109, 2.6 Biological Experiment).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a liquid polymeric implant comprising an anticancer agent homogeneously dispersed into a biodegradable polymer matrix, as taught by Domb, substitute the polymer matrix of Domb with the terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction) that allows prolonged release of a biodegradable composition, as suggested by Hampl, and produce the instant invention.

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One of ordinary skill in the art would have been motivated to do this because Hampl teaches that terpolymer of GA-M-DLLA allows the prolonged release of the active ingredient over 15 weeks (Abstract and Figures 4 and 5). It would have been obvious to substitute the biodegradable polymer matrix of Domb with the biodegradable polymer matrix of Domb because both matrices allow controlled release of the active ingredient.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 12, the biodegradable composition with prolonged release would have been obvious over the biodegradable composition with prolonged release taught by Hampl (Abstract and Page 108, Table 1). The limitation of the plastic viscous antitumor composition would have been obvious over the oligoester composition taught by Hampl (Abstract). This oligoester composition will intrinsically have the plastic viscous attributes as instantly claimed. The limitation of the antitumor composition and the antitumor agent would have been obvious over the antitumor composition comprising anti-cancer agents (Cisplatin and Paclitaxel) that are homogeneously distributed in the polymer matrix, as taught by Domb (Page 4, [0046]). The limitation of the “antitumor agent for administration into tissues” would have been obvious over the antitumor composition comprising Cisplatin and Paclitaxel that is

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injected into the tumor, as taught by Domb (Page 4, [0046]) in view of the subcutaneous administration of the composition to mice, as taught by Hampl (Page 109, 2.6 Biological Experiment). The limitation of the biodegradable oligoester would have been obvious over the terpolymer (GA-M-DLLA) taught by Hampl (Abstract). The limitation of the  $M_n$  from 650 to 7,500, the  $M_w$  from 800 to 10,000, and the  $T_g$  from -35 to 45°C, would have been obvious over the  $M_n$  of 2.20Kda,  $M_w$  of 3.95 kDa, and  $T_g$  of 20°C, as taught by Hampl (Page 108, Table 1). The limitation of the polycondensation reaction would have been obvious over the GA-M-DLLA that was prepared by polycondensation reaction, as taught by Hampl (Page 108, 2.2 Preparation of oligoesters). The limitation of the polyhydric alcohol containing at least 3 hydroxy groups would have been obvious over the mannitol in the oligoester taught by Hampl (Abstract). The limitation of the aliphatic  $\alpha$ -hydroxy acid would have been obvious over the DL-lactic acid in the oligoester taught by Hampl (Abstract). The molar ratio of the polyhydric alcohol to aliphatic  $\alpha$ -hydroxy acid would have been obvious over the ratio of mannitol to DL-lactic acid (0.9:45.05) taught by Hampl (Page 108, Table 1). The limitation of the form of the composition as a homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion would have been obvious over the liquid polymer implant taught by Domb (Page 4, [0046]).

### ***Response to Arguments***

7. Applicant's arguments, see Page 5, filed 10/23/09, with respect to the rejection of claim 12 under 35 USC § 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Domb (US 2004/0057970 A1) have been fully considered but are not persuasive.

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Applicant disagrees with the interpretation of the content of Hampl et al.

Applicant argues that: "Hampl et al. describes, in fact, only two specific ter(co)polymers having mannitol as bridge component, i.e. terpolymer of DL-lactic acid, glykolic acid and mannitol (GA-M- DLLA) and copolymer of DL-lactic acid and mannitol (M-DLLA). Both ter(co)polymers are evidently non-plastic/viscous under normal temperature and pressure conditions. Even though this non-plastic/viscous character of both ter(co)polymers is not expressly mentioned in Hampl et al., this non-plastic/viscous character of both Hampl et al.'s ter(co)polymers follows from the fact that their only their use - as mentioned by Hampl et al. - is to form a microcapsule shell. This use clearly excludes the possibility of a plastic/viscous character of Hampl et al.'s ter(co)polymer ... Hampl et al. neither mentions nor suggests the oligoesters based on DL-lactic acid, glykolic acid and mannitol being plastic viscous under normal temperature and pressure conditions."

This is not persuasive because the plastic viscous nature of the biodegradable oligoester is a physical property that is associated with the oligoester. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. Please see MPEP 2112.01.

Applicant argues that: "The fact that the specific values of Mn, Mw and Tg for the Hampl et al.'s non-plastic/viscous ter(co)polymer as provided in Table 1 of Hampl et al. fall into the respective ranges of the present claim 12 is not particularly relevant since the plastic/viscous oligoesters of the presently-claimed invention are additionally delimited by the fact that they must be plastic/viscous. This additional obligatory



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condition inherently excludes the Hampl et al.'s non-plastic/viscous ter(co)polymers from the definition of the present claim 12. Even though the plastic/viscous consistency of the oligoesters used in the presently-claimed invention inherently follows from the plastic/viscous consistency of the claimed composition (the plastic/viscous consistency of the claimed composition is clearly provided by the oligoester carrier itself rather than by the antitumor agent), the Applicants have emphasized this reality by highlighting that the carrier is "plastic viscous." The structural difference between the Hampl et al.'s ter(co)polymers and those of the presently-claimed invention (which difference simultaneously conditions the substantially solid and plastic/viscous state of both types of oligoesters) is based on the fact that the oligoesters of the presently-claimed invention have a higher branching degree  $g'$  as noted in Applicants' reply to the previous official action."

This is not persuasive because claims do not recite a requirement for a particular degree of branching. All the limitations of the biodegradable prolonged release oligoester composition of instant claim 12 are obviated by the teachings of Hampl. One of ordinary skill in the art would find it obvious to modify conditions (temperature, pressure, reaction time, as well as degree of branching of the oligoester) of the polycondensation reaction based on the guidance of Hampl, during the process of routine experimentation, since these are manipulatable conditions. It would have been obvious to one of ordinary skill in the art at the time of invention to determine all optimum and operable conditions (e.g. temperature, pressure, reaction time), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. "[W]here the

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general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955). Please see MPEP § 2145.05.

Applicant argues that Hampl et al. only taught non-plastic/viscous oligoesters which are, as carriers, absolutely unadaptable for the plastic viscous composition presently called for and which were used by Hampl et al. to form non-liquid microcapsule shells.

This is not persuasive because the oligoester composition of Hampl can be modified by one of ordinary skill in the art and it will intrinsically have the plastic viscous attributes as instantly claimed.

Applicant argues that even though the person skilled in the art may have modified the Hampl et al.'s preparative conditions in order to try to prepare some plastic/viscous oligoesters of Hampl et al.'s kind, he could not have a reasonable expectation of success in the absence of any suggestion from Hampl et al.

This is not persuasive because Hampl is combined with Domb, and Domb teaches liquid polymeric implant composed of a biodegradable matrix. One of ordinary skill in the art would look to the teachings of Domb to produce an implantable (liquid or plastic or viscous) matrix.

Applicant argues that it was not obviously detectable from Hampl et al. that the preferred release regime promoted by the acid degradation products further catalyzes the degradation of the presently-claimed invention's plastic viscous composition.

Applicant argues that the preferred release regime promoted by the fact that the acid degradation products further catalyze the degradation of the invention composition was

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not obviously detectable from Domb since the degradation of Domb's composition takes place under a quite different chemical mechanism.

Applicant's arguments regarding the acid degradation products and catalysis mechanism are not commensurate in scope with the instant claims. The features relied upon by Applicant are not recited in the instant claims. The structural components of the composition are obviated by the teachings of Domb and Hampl. The catalysis mechanism associated with the composition would therefore also be necessarily obviated by the teachings of the references.

Applicant argues that the presently-claimed composition is not obvious in view of the combination of Hampl et al. and Domb, since if the Domb's polyanhydride viscous polymer matrix is replaced with Hampl et al.'s non-viscous ter(co)polymer matrix, no viscous composition is obtained.

This is not persuasive because the plastic viscous nature of the biodegradable oligoester is a physical property that is associated with the oligoester. A chemical composition and its properties are inseparable. Therefore, if the prior art (Hampl) teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. Please see MPEP 2112.01.

Therefore, the rejection of 07/14/09 is maintained.

***Claim Rejections - 35 USC § 103***

8. Claims 13-17 **remain** rejected under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Domb (US 2004/0057970 A1) and further in view of Berggren et al. (US 5,783,205).

The teachings of Hampl and Domb are stated above.

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Hampl and Domb do not expressly teach a composition further comprising a liquid biocompatible plasticizer.

Berggren teaches a drug delivery device (injection) comprising an antibiotic drug and a matrix comprising a bioerodible polymer “selected from polylactic acid, polyglycolic acid, copolymers of lactic acid and glycolic acid, polylactide-co-glycerate, polyglycolide-co-glycerate and poly(orthoesters), or a bioerodible oligomer selected from oligomers of hydroxycarbonic acids and oligomers of glycolic acid and/or lactic acid and their derivatives with alcohols and/or carbonic acids” (Col. 4, lines 48-57). “The delivery device of the invention may also optionally include an amount of a plasticizer to alter the viscosity of the matrix material so that it falls within the range required by the present invention ... Suitable biocompatible plasticizers include ... triethyl citrate, acetyl triethyl citrate ... propylene oxide ... when a plasticizer is included in the matrix material, it is generally present in an amount of from about 5 to about 30 wt %, preferably from about 7 to about 20 wt %” (Col. 9, lines 45-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a liquid polymeric implant comprising an anticancer agent homogeneously dispersed into a biodegradable polymer matrix, as taught by Domb, substitute the polymer matrix of Domb with the terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction) that allows prolonged release of a biodegradable composition, as suggested by Hampl, further combine it with the use of a plasticizer in a biodegradable and injectable composition, as taught by Berggren, and produce the instant invention.

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One of ordinary skill in the art would have been motivated to do this because Berggren teaches that the use of a plasticizer depends on the matrix material used, for example for keeping the material from becoming too hard and brittle (Col. 9, lines 48-53) and that for altering the viscosity of the matrix material so that it falls within the range required (Col. 9, lines 45-67).

Regarding instant claims 13-14, the limitations of the one liquid biocompatible plasticizer and the plasticizer soluble in the carrier would have been obvious over the plasticizer used in the matrix material to alter the viscosity, as taught by Berggren (Col. 9, lines 45-67). One with ordinary skill in the art would know that in order to successfully alter the viscosity of the matrix material, the plasticizer used would have to be soluble in the matrix material. The limitation of the weight ratio of the plasticizer to oligoester (claim 13) would have been obvious over the ratio of triethyl citrate to PLGA, which ranges from 1:4.33 to 1:9, as shown in examples 2-5 by Berggren (Col. 13, Table B, lines 55-63).

Regarding instant claim 15, the limitation of an agent influencing the kinetics of the release of the antitumor agent would have been obvious over the "drug release-rate regulating agents" taught by Berggren (Col. 10, lines 1-2).

Regarding instant claim 16, the limitation of a stabilizer of the antitumor agent or carrier would have been obvious over the stabilizers taught by Berggren (Col. 10, lines 1-3).

Regarding instant claim 17, the limitation of heating an antitumor agent, a carrier, optionally a plasticizer, an agent influencing the kinetics of the release of the antitumor agent, and a stabilizer of the antitumor agent or a stabilizer, would have been obvious

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over the composition taught by Hampl (Abstract), in view of the antitumor agents taught by Domb (Page 4, [0046]), and further in view of the teaching by Berggren that the “matrix material is heated to soften the material to a point where it becomes flowable and can be delivered at a physiologically compatible elevated temperature into a biological pocket” (Col. 4, lines 14-17). One with ordinary skill in the art would heat the mixture depending on the constituents (polymer matrix, active ingredient) and depending on the administration site. The recited temperature range of 35 to 75°C would have been an obvious variant during the process of routine experimentation, unless there is evidence of criticality or unexpected results.

### ***Response to Arguments***

9. Applicant’s arguments, see Page 13, filed 10/23/09, with respect to the rejection of claims 13-17 under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Domb (US 2004/0057970 A1) and further in view of Berggren et al. (US 5,783,205) have been fully considered but are not persuasive.

Applicants argue that “both Hampl et al. and Domb both individually and in combination fail to disclose or suggest critical elements claimed in currently amended independent claim 12, from which all other claims depend. These elements are not supplied by Berggren et al.

This is not persuasive because all the limitations of the biodegradable prolonged release oligoester composition of instant claim 12 are obviated by the teachings of Hampl and the combination of Domb and Hampl renders the limitations of an anticancer agent in a biodegradable oligoester composition. The deficiency in the combination of

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Domb and Hampl is that of a liquid biocompatible plasticizer. This deficiency is remedied by Berggren and the references are properly combined because Berggren teaches that the use of a plasticizer depends on the matrix material used, for example for keeping the material from becoming too hard and brittle and that for altering the viscosity of the matrix material so that it falls within the range required (Col. 9, lines 45-67).

Therefore, the rejection of 07/14/09 is maintained.

***Conclusion***

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached at 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/  
Examiner, Art Unit 1615

/Robert A. Wax/  
Supervisory Patent Examiner  
Art Unit 1615